Evaluation of the Safety and Efficacy of Using Insulin-like Growth Factor-1 in Patients With a Heart Attack (RESUS-AMI)

Published: 27-08-2014
Last updated: 20-04-2024

The primary objective of the study will be to evaluate two low doses of a single intracoronary injection of rhIGF-1 compared with saline placebo on global LVEF by cardiac MRI and for safety (hypoglycaemia) in select subjects with STEMI and severe...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Coronary artery disorders
Study type	Observational invasive

Summary

ID

NL-OMON40846

Source
ToetsingOnline

Brief title
RESUS-AMI

Condition

- Coronary artery disorders

Synonym
acute myocardial infarction with LVEF< 30%, heart attack with heartfailure

Research involving
Human

Sponsors and support

Primary sponsor: University college Cork, Centre for Research in Vascular Biology Bio

Sciences Institute
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: AMI, Growth factor-1, intracoronary, STEMI

Outcome measures

Primary outcome

The primary efficacy endpoint to be measured during this study is the percent

change from baseline in LVEF at 8 weeks measured by quantitative cardiac MRI

Secondary outcome

Secondary efficacy endpoints are:

* Change from baseline in regional left ventricular (LV) wall motion and

thickness at Week 8 by cardiac MRI

* Change from baseline in LV mass, LV end-systolic volumes, LV end-diastolic

volumes, LV stroke volume and cardiac output (by cardiac MRI and

echocardiography) at Week 8

* Change from baseline in infarct size at Week 8

* NYHA class at Week 8, Month 6 and Month 12

* Change from baseline in LVEF,LV end-systolic volumes, LV end-diastolic

volumes, and regional wall motion abnormalities at Month 6 and Month 12

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SAFETY ENDPOINTS

The primary safety endpoint is serum glucose measurement obtained 30 minutes

and 1 hour after study drug administration

Secondary safety endpoints are:

* Incidence of hypotension or arrhythmias at time of study drug administration

* Incidence of clinical events: cardiovascular and all-cause death, recurrent myocardial infarction, severe recurrent ischemia, target vessel revascularisation, hospitalisation for worsening heart failure, stroke and arrhythmia through month 12

* Treatment-related adverse events

* Incidence of abnormal clinical laboratory measurements through hospitalisation for index event

Study description

Background summary

There are currently over 3 million ST-elevation myocardial infarcts (STEMIs) worldwidei, approximately 20% of which progress to chronic heart failure (HF) contributing enormous human cost in terms of morbidity and mortality and substantial economic cost in terms of long term care. Reduction in infarct size after STEMI remains an untouched treatment frontier. Improvement in left ventricular ejection fraction (LVEF) from less than 30% to greater than 35% would obviate the need for automatic cardiac defibrillator implantation in these patients, reducing health care costs significantly. Moreover the savings in returning such patients to active lives and reducing subsequent hospital admissions and chronic heart failure treatment may be estimated at 10 to 50 million euro/year in Ireland alone.ii
Insulin-like growth factor-1 (IGF-1) is a peptide similar in structure to insulin and has been known for more than two decades as a key regulator of cardiac structure. More recently key functions in cardiomyocyte homeostasis for this growth factor have been described including promotion of growth, inhibition of apoptosis and potentiation of calcium signaling. The most intriguing cardiac function of IGF-1 from a therapeutic perspective remains its prosurvival effect which is mediated in large part through the PI3kinase/Akt signaling pathway. IGF-1 when produced locally in the heart is a potent cardiac survival factor.iii In the circulation free IGF-1 accounts for approximately 1% of the total IGF-1 which is predominantly bound in serum to insulin-like growth factor binding proteins.iv The half life of injected IGF-1 is approximately 14 minutes in humans. Based on known signaling events associated with activation of the IGF-1 receptor, the actions of IGF-1 on cells includes, inter alia,

effects on cell size, proliferation, apoptosis, glucose metabolism, intracellular calcium regulation as well as contractility. IGF-1 pro-survival signaling is complex but following receptor binding and phosphorylation insulin receptor substrate is recruited, phosphorylated and subsequently PI3Kinase /Akt activated which inhibits propapoptotic initiators such as Bad.v
There is evidence from human studies that relatively low circulating IGF-1 levels in patients post-myocardial infarct (MI) has an adverse effect on left ventricular (LV) remodelling.vi The first uncontrolled clinical trial to suggest positive IGF-1-like effects in HF patients involved administration of human growth hormone (hGH) the tissue effects of which are mediated through IGF-1.vii Subsequent randomised controlled trials however showed no sustained benefit of hGF and indeed chronic administration was associated with a variety of side effects including bone tenderness, arthralgias, edema, orthostatic hypotension and tachycardia.viii Consequently interest in use of IGF-1 in cardiac disease diminished.
Recently, Caplice et al have shown in a porcine model, a single low dose of recombinant IGF-1 (600pg/animal) administered via the coronary artery 2hrs after reperfusion of an acute MI had potent cardiac repair effects. At 30 minutes post IGF-1 therapy, IGF-1 receptor but not insulin receptor phosphorylation was significantly augmented in the infarct border zone but not the remote zone. This was associated with significant increase in phosphorylation of Akt and Erk signaling pathways. Consistent with activation of survival pathways in the infarct zone, apoptosis was also significantly reduced in vivo by low dose IGF-1 compared to vehicle at 24 hours post infarct. Acute low dose IGF-1 effects on cell survival were associated at 8 weeks with a very significant decrease in infarct size and a marked improvement in end systolic and end-diastolic volumes and systolic ejection fraction. These salutary improvements in LV remodeling were confirmed by marked improvement in wall motion and wall thickening abnormalities seen on CT in the IGF-1 treated compared to the control treated animals (data unpublished). These data underscore a hitherto unrecognized acute effect of low dose IGF-1 which may have profound implications for cardiac repair post-MI

Study objective

The primary objective of the study will be to evaluate two low doses of a single intracoronary injection of rhIGF-1 compared with saline placebo on global LVEF by cardiac MRI and for safety (hypoglycaemia) in select subjects with STEMI and severe left ventricular dysfunction undergoing PCI.

Study design

This is a randomised, placebo-controlled, double-blind study to assess the safety and efficacy of intracoronary recombinant human insulin-like growth factor-1 (rhIGF-1) administered during percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI). Subjects will be consented

prior to PCI and following successful reperfusion and stenting, 45 subjects with TIMI 3 flow in the infarct related artery (IRA) and a left ventricular ejection fraction (LVEF) <40% will be randomised 1:1:1 to a single intracoronary injection of 1.5 ng or 15 ng rhIGF or saline placebo. Randomisation will be stratified by presence of diabetes mellitus. Subjects will undergo cardiac magnetic resonance imaging (MRI) and echocardiogram within 24 hours (baseline) of study drug administration to assess global LVEF. Phone follow-up to assess for clinical and adverse events will occur at day 30. Repeat cardiac MRI, echocardiogram and clinical and adverse event assessments will occur at a Week 8 visit and repeat echocardiogram and clinical and adverse event assessments will occur at Month 6 and Month 12 visits.

Study burden and risks

WHAT IS INVOLVED IN THE STUDY AND WHAT WILL I BE ASKED TO DO?
If you take part in this study, you will be asked to read and sign a consent form. After you sign the consent form, the study procedures below will take place:

* A member of the study team will ask you questions about your medical history. Your medical record will be examined and your cardiologist may be asked questions to collect data regarding your procedure and hospital stay.

* A brief physical examination of your heart, lungs, pulse and blood pressure will be done.

* Women able to have children will have a urine or blood pregnancy test to see if they are pregnant. Pregnant females are not allowed in the study.

* During your angioplasty procedure, if your consultant cardiologist has opened the blocked artery that has caused your heart attack, he/she will check your heart muscle function by injecting contrast into your heart chamber. This is a standard procedure. If he/she determines that your heart muscle function is weak and you meet all the other criteria for the study, you will be assigned to receive either mecasermin (the study drug) at one of two doses or a placebo infusion in the blocked artery over 30 seconds. You will have an equal chance of receiving one of the three treatments. Neither your consultant nor study team members will know which treatment you received however your consultant can get this information if needed. If your heart muscle is not weak enough to meet the criteria for the study, your participation is finished and no further study tests will be done.

* A half hour and one hour after the procedure your blood will be drawn to check your blood sugar. Other regular blood work may be drawn at the same time to monitor your treatment for your heart attack. Your blood pressure and pulse will be checked frequently for the first hour after your procedure.

* Within 24 hours of your procedure you will undergo a cardiac MRI and echocardiogram (a heart ultrasound) to look at your heart function. The study team will continue to review your medical records and ask you how you are feeling during your hospital stay.

* Approximately 30 days after your procedure, a study team member will call you at home to ask you about your health since your hospital stay.

* Eight weeks after your procedure you will have another cardiac MRI and echocardiogram and a study member will ask you about your health.

* Six months and one year after your procedure you will have another echocardiogram and a study member will ask you about your health.

Contacts

Public
University college Cork, Centre for Research in Vascular Biology Bio Sciences Institute

college road room 2.40
Cork 0000
IE
Scientific
University college Cork, Centre for Research in Vascular Biology Bio Sciences Institute

college road room 2.40
Cork 0000
IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age 18 * 75
2. Subject presents to hospital within 2-12 hours of the onset of myocardial ischemic pain of at least 30 minutes duration
3. Twelve-lead electrocardiogram (ECG) reveals one of the following: ST-segment elevation * 0.1 mV in two or more limb leads, or * 0.2 mV in two or more contiguous precordial leads indicative of acute myocardial infarction, or left bundle-branch block
4. Undergoing PCI for STEMI
5. LVEF during PCI < 40%
6. TIMI flow grade 3 in IRA following reperfusion and stenting

Exclusion criteria

4.3 EXCLUSION CRITERIA
Subjects having any of the following criteria will not be enrolled in the study:
1. History of prior myocardial infarction
2. Prior history of heart failure, left ventricular dysfunction or cardiomyopathy
3. Active or suspected neoplasia
4. Known impaired liver function
5. Cardiogenic shock (SBP<80mm Hg requiring pressors or IABP)
6. Estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73m2
7. History of hypoglycaemia requiring hospitalisation
8. History of primary insulin growth factor-1 deficiency or growth hormone disorders including acromegaly
9. Contraindication to cardiac MRI (e.g. pacemaker, implanted cardiac defibrillator or other magnetically activated device, aneurysm clips, claustrophobia)
10. Pregnancy (for women of childbearing potential, have a negative pregnancy test at screening) or nursing mothers
11. Known allergy to study drug or any of its inactive ingredients
12. Treatment with another investigational agent within 30 days of enrolment
13. Subjects unable or unwilling to comply with follow-up requirements of study
14. Subjects unable to provide written informed consent

Study design

Design

Study phase:	3
Study type:	Observational invasive

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	increlex
Generic name:	mecasermin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-08-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-02-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-05-2015
Application type:	Amendment

Review commission: METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-000480-27-NL
ClinicalTrials.gov	NCT01438086
CCMO	NL47868.058.14